out the bulk of ubiquitin recognition functions when proteasomes are not overloaded. These data suggest that an Rpn13 inhibitor should have a wider therapeutic window than inhibitors of proteolytic sites (Figure 1B). Taken together, this study by Anchoori et al. (2013) validates the proteasome ubiquitin receptor Rpn13 as a druggable target and opens a new road to extend the therapeutic application of proteasome inhibitors to the treatment of solid tumors.

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The Evolution of Tumor Classification: A Role for Genomics?

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Lung cancers are divided into four types according to their histologic appearance. Therapeutic decisions are partly based on histology. A recent study indicates that certain molecular alterations associate with histology and that therapies directed to these molecular changes improve outcome, indicating that genomic information should be incorporated into future tumor classification.

Lung cancers are the most common cause of cancer death worldwide. For many years, lung cancer histologies have been determined according to the World Health Organization (WHO) classification based primarily on the light microscopic appearance of the malignant cells (adenocarcinoma, squamous carcinoma, large cell carcinomas, and small cell carcinoma). The most recent proposed WHO modifications reclassified some adenocarcinomas into adenocarcinoma in situ, incorporating some prior bronchioalveolar carcinomas and minimally invasive or invasive carcinomas with specification of the predominant histologic pattern (Travis et al., 2011). In past years, small cell carcinomas mixed with large cell carcinoma (the so-called 22/40 subtype) were distinct within the small cell classification, but later revision classified these as either small cell carcinoma or large cell undifferentiated carcinomas with neuroendocrine features (Travis et al., 2004). Mixed small cell/adenocarcinoma remained as a histologic designation. Tumors where no differentiation could be determined by histologic appearances or immunohistochemical staining for adenocarcinoma or squamous cell carcinoma features were designated as large cell undifferentiated carcinomas. The WHO classification is scheduled for revision in 2014.

Enter genomic testing. The paper from the Clinical Lung Cancer Genome Project (CLCGP) and Network Genomic Medicine (NGM) team sheds considerable light on the relationship between histologic appearance and genomic abnormalities [The Clinical Lung Genome Project (CLCGP) and Network Genomic Medicine (NGM), 2013]. The authors report that almost all cases of large cell undifferentiated carcinomas could be reclassified and assigned to one of the other histologic types based on both immunohistochemistry and genomic alterations. These findings have considerable relevance to patients with a histologic diagnosis of large cell carcinoma. Clinically, these patients are currently grouped with patients with adenocarcinomas and treated with cytotoxic

chemotherapy (Scagliotti et al., 2008). Going forward, patients with large cell carcinoma that have genetic features associated with squamous cancers should be considered for clinical trials with tailored therapies for squamous cancer (e.g., FGFR amplification or SOX2 or DDR2 mutation) or cytotoxic chemotherapy for squamous cancer (i.e., patients with squamous cancers should not receive pemetrexed or bevacizumab) (Scagliotti et al., 2008; Johnson et al., 2004). In contrast, large cell carcinomas assigned to the group with adenocarcinoma-type genetic features should receive a specific adenocarcinoma driver therapy (e.g., EGFR or ALK tyrosine kinase inhibitors) if a driver is present or a cytotoxic chemotherapy for adenocarcinoma (e.g., pemetrexed) if no drivers are identified. Large cell carcinomas with neuroendocrine features should be treated as small cell carcinomas.

Many questions remain, even with this extensive genetic analysis. Should all lung cancer patients undergo extensive genetic testing and/or next-generation sequencing? Although this paper shows that this approach is increasingly feasible and the advantages of providing diagnostic, prognostic and treatment related information in one package becomes increasingly attractive, the answer is probably not yet. Current guidelines suggest testing all adenocarcinomas or tumors with adenocarcinoma components for *EGFR* or *ALK* alterations (Lindeman et al., 2013). This study from the CLCGP and NGM would indicate that this guideline would be relevant for large cell carcinomas as well, because many would have genetic features similar to adenocarcinoma. The guideline was developed in large part because EGFR and ALK TKIs were shown to be superior to chemotherapy in patients with lung adenocarcinoma with *EGFR* or *ALK* alterations, respectively (Lindeman et al., 2013). Guideline recommendations for testing the other genetic alterations found in adenocarcinomas will await clinical trials establishing efficacy of oncogene-targeted therapies in these subgroups. Similarly, routine testing for the genetic alterations typically found in squamous carcinomas or neuroendocrine carcinomas (small cell or large cell) must await clinical trials showing the efficacy of targeted therapy. These data should be considered in the revised WHO classification, especially as they relate to large cell carcinomas.

Of course, the primary reason for classification of tumors is to better assign appropriate therapy for our patients. In the end, the histologic subtype may be of little importance if an oncogene is identified in a tumor sample and the tumor can be treated effectively with a targeted therapy. Indeed, this type of genomic reclassification may one day extend beyond the current boundaries of organ-specific tumor classification. The term ''ALKoma'' was recently proposed, and early data suggest that multiple different tumor types harboring ALK gene fusions can respond to an ALK TKI (Mano, 2012).

These data strongly suggest that clinical treatment decisions must take staging classification, histology, and genetic features into consideration before assigning therapy. They also highlight the necessity of more widespread genetic analyses in the clinical trials of all lung cancer histologies.

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